UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,645	03/20/2002	Stefan Anker	101195-64	6782

27387 7590 11/21/2005

NORRIS, MCLAUGHLIN & MARCUS, P.A.
875 THIRD AVE
18TH FLOOR
NEW YORK, NY 10022

EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,645	ANKER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,17,18,21,25-27,53,78,82,83 and 85-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,17,18,21,25-27,53,78,82,83 and 85-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/23/05 has been entered.

2. Claims 1-2, 6, 17-18, 21, 25-27, 53, 78, 82-83, and 85-87 are pending and are being acted upon in this Office Action.

3. Claim 2 is objected to because "acute *and* chronic" on line 1 should have been "acute or chronic".

4. Claim 6 is objected to because "CD14" should have been "soluble CD14".

5. The listing of references in the specification on pages 47-50 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 6, 17-18, 21, 25-27, 53, 78, 82-83, and 85-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of ameliorating or treating endotoxin-mediated TNF-α production in acute and chronic heart failure, the method comprising the steps of measuring the level of TNF-α from blood sample taken from the patient, and administering to the patient a therapeutically effective amount of ursodeoxycholic acid when the levels of TNF-α is elevated, and (2) a pharmaceutical formulation comprising ursodeoxycholic acid and a diuretic, **does not** reasonably provide enablement for (1) a method of

determining, ameliorating and treating any heart failure in a human patient comprising the steps of measuring the level of any cytokines or any inflammatory marker or any cytokine production in the blood of the patient, and if any such level is elevated, administering to the patient a therapeutically effective amount of any bile acid such as ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid, (2) the said method wherein the heart failure is an acute or chronic congestive heart failure due to cardiomyopathy of unknown reason, any coronary artery disease, any valvular disease, any hypertrophic obstructive cardiomyopathy, any viral myocarditis or any genetic cardiomyopathy or dilated cardiomyopathy, (3) the method of determining, ameliorating and treating any heart failure in a human patient comprising the steps of measuring the level of any cytokine, the level of endotoxin (LPS), TNFα and CD14 or any cytokine production in the blood of the patient, and if any such level is elevated, administering to the patient a therapeutically effective amount of any bile acid such as chenodeoxycholic acid, dehydrocholic acid and cholic acid, (4) the method mentioned above wherein the bile acid is able to inhibit any response by any cell to endotoxin (LSP), (the method mentioned above wherein the bile acid is able to decrease any cytokine production by any cell in response to endotoxin (lipopolysaccharide, LPS), (5) the said method wherein the bile acid such as ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid are able to reduce the permeability of the gut wall to bacteria and/or endotoxin (lipopolysaccharide, LPS), (6) the said method wherein the bile acid is administered orally, intravenously or rectally, (7) a method of reducing elevated levels of LPS in human blood of patients by administering any amount of bile acid selected from the group consisting of ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid, (8) the method of reducing elevated levels of LPS in human blood of patients by administering any amount of bile acid selected from the group consisting of ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid wherein the patients with cachexia due to liver cirrhosis, and (9) the method of reducing elevated levels of LPS in human blood of patients by administering any amount of bile acid selected from the group consisting of ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid wherein the bile acid is administered intravenously, rectally, or orally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of ameliorating or treating endotoxin-mediated immune activation in acute or chronic heart failure, the method comprising the steps of measuring the level of TNF-α, endotoxin, and soluble CD14 from blood sample taken from the patient, and administering to the patient ursodeoxycholic acid or a combination of ursodeoxycholic acid and diuretics when the levels of TNF-α, endotoxin or soluble CD14 is elevated. The specification further discloses a method of reducing elevated levels of LPS induced TNF-α in human by administering ursodesoxycholic acid to the human patient with cachexia due to liver cirrhosis (page 45, Example 12).

The specification does not teach how to determine and treat any heart failure in human such as any acute or chronic congestive heart failure to any cardiomyopathy of unknown reason, any coronary artery disease, any valvular disease, any hypertrophic obstructive cardiomyopathy, any viral myocarditis or any genetic cardiomyopathy or dilated cardiomyopathy by measuring the level of any cytokine, any inflammatory marker or its production by administering to the patient any bile acid such as chenodeoxycholic acid, dehydrocholic acid and cholic acid. The specification does not teach which elevated cytokines other than TNF-α, endotoxin, and soluble CD14 are associated with which heart failure mentioned above. Further, there is a lack of guidance as to which elevated inflammatory marker are associated with which heart failure in humans. There is a lack of guidance as to the effective amount of all bile acid to be administered to patient with all kinds of heart failure. Other than ursodeoxycholic acid or combination of ursodeoxycholic acid and diuretics, there is a lack of in vivo working examples demonstrating the other bile acid such as chenodeoxycholic acid, dehydrocholic acid and cholic acid are effective for treating all kinds of heart failure, much less for reducing the elevated levels of cytokines, inflammatory markers, cytokine production.

Greve et al, PTO 1449, teach not all bile acids are capable of reducing LPS mediated TNF production. Greve et al teach deoxycholic acid (DCA) in the concentration used appeared to be a strong inhibitor of TNF release by human monocytes whereas chenodeoxycholic acid

(CDCA) is less effective and ursodeoxycholic acid (UDCA) is not effective at any concentration (see page 456, col. 2, Results, Figure 1, page 456, Figure 2, in particular).

With regard to claims 82-83, and 85-87, there is no evidence of record showing that administering any bile acid such as urosodesoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid to any human patient, or any human patient with cachexia due to liver cirrhosis would resulted in reducing the elevated levels of LPS. The specification discloses elevated endotoxin levels were normalized by prolonged diuretic treatment in patient with heart failure having peripheral edema (page 37, lines 27-28).

Given the unlimited number of patient population having all sort of heart failures, the unlimited number of cytokines and inflammatory markers, it is unpredictable which bile acid is capable of reducing the elevated levels of which cytokine, which bile acid is capable of reducing the elevated levels which inflammatory maker or its production, in turn, would be useful for treating any type of heart failure. The specification is silent which cytokines is elected in "genetic cardiomyopathy". If the heart failure is genetically predisposed, there is no evidence of record that the claimed method could treat such condition simply by administering any bile acid such as the ones cited in claim 1.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments and the declaration of Stefan Anker filed 9/23/05 have been fully considered but are not found persuasive. Applicants' position is that claim 1 has been amended to recite the specific bile acid and no longer reads on preventing heart failure comprising administering to the patient any or all compound. The specification (Example 1) shows the levels of endotoxin, LPS, TNFα and CD14 are elevated in patient suffering from chronic heart failure. The conclusion of Example 2 that UDCA may be tested in patient with edema or with cardiac cachexia. Example 10 of the specification shows that LPS-stimulated cytokine production can be

inhibited by application of UDCA. In addition, the attached Exhibits 1 and 2, which show experiments conducted in vivo for the treatment of chronic heart failure. Exhibit 1 shows an in vivo study conducted by comprising the administration of UDCA to three patients suffering from chronic heart failure ameliorates the overall performance of said patients. In another in vivo experiment, Exhibit 2 shows the importance of a reduction of LPS in patients suffering from cardiovascular and hemodynamic instability. One of skilled in the art would recognize that each of the three additional claimed bile acids (compared to UDCA) can be used in equal measure, due to their close structural and functional similarity.

In response, although claim 1 has been amended, the claimed method still encompasses treating any heart failure by measuring any cytokines, any inflammatory markers, any cytokines and any inflammatory marker production and administering to the patient with such as ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid. Further, the Exhibits 1 and 2 that suppose to accompany the amendment filed 9/23/05 are not found.

The specification discloses only a method of ameliorating or treating endotoxin-mediated immune activation in acute or chronic heart failure, the method comprising the steps of measuring the level of TNF-α, endotoxin, and soluble CD14 from blood sample taken from the patient, and administering to the patient ursodeoxycholic acid or a combination of ursodeoxycholic acid and diuretics when the levels of TNF-α, endotoxin or soluble CD14 is elevated. The specification further discloses a method of reducing elevated levels of LPS induced TNF-α in human by administering ursodesoxycholic acid to the human patient with cachexia due to liver cirrhosis (page 45, Example 12).

The specification does not teach how to determine and treat any heart failure in human such as any acute or chronic congestive heart failure to any cardiomyopathy of unknown reason, any coronary artery disease, any valvular disease, any hypertrophic obstructive cardiomyopathy, any viral myocarditis or any genetic cardiomyopathy or dilated cardiomyopathy by measuring the level of any cytokine, any inflammatory marker or its production by administering to the patient any bile acid such as chenodeoxycholic acid, dehydrocholic acid and cholic acid. The specification does not teach which elevated cytokines other than TNF-α, endotoxin, and soluble CD14 are associated with which heart failure mentioned above. Further, there is a lack of guidance as to which elevated inflammatory marker are associated with which heart failure in humans. There is a lack of guidance as to the effective amount of all bile acid to be administered to patient with all kinds of heart failure. Other than ursodeoxycholic acid or combination of

ursodeoxycholic acid and diuretics, there is a lack of in vivo working examples demonstrating the other bile acid such as chenodeoxycholic acid, dehydrocholic acid and cholic acid are effective for treating all kinds of heart failure, much less for reducing the elevated levels of cytokines, inflammatory markers, cytokine production.

Greve et al, PTO 1449, teach not all bile acids are capable of reducing LPS mediated TNF production. Greve et al teach deoxycholic acid (DCA) in the concentration used appeared to be a strong inhibitor of TNF release by human monocytes whereas chenodeoxycholic acid (CDCA) is less effective and ursodeoxycholic acid (UDCA) is not effective at any concentration (see page 456, col. 2, Results, Figure 1, page 456, Figure 2, in particular).

With regard to claims 82-83, and 85-87, there is no evidence of record showing that administering any bile acid such as urosodesoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid to any human patient, or any human patient with cachexia due to liver cirrhosis would resulted in reducing the elevated levels of LPS. The specification discloses elevated endotoxin levels were normalized by prolonged diuretic treatment in patient with heart failure having peripheral edema (page 37, lines 27-28).

Given the unlimited number of patient population having all sort of heart failures, the unlimited number of cytokines and inflammatory markers, it is unpredictable which bile acid is capable of reducing the elevated levels of which cytokine, which bile acid is capable of reducing the elevated levels which inflammatory maker or its production, in turn, would be useful for treating any type of heart failure. The specification is silent which cytokines is elected in "genetic cardiomyopathy". If the heart failure is genetically predisposed, there is no evidence of record that the claimed method could treat such condition simply by administering any bile acid such as the ones cited in claim 1.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

8. Claims 1-2, 6, 17-18, 21, 25-27, 53, 78, 82-83, and 85-87 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of determining, ameliorating and treating any heart failure in a human patient comprising the steps of measuring the level of any cytokines or any inflammatory marker or any cytokine production in the blood of the patient, and if any such level is elevated, administering to the patient a therapeutically effective amount of any bile acid such as ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid, (2) the said method wherein the heart failure is an acute or chronic congestive heart failure due to cardiomyopathy of unknown reason, any coronary artery disease, any valvular disease, any hypertrophic obstructive cardiomyopathy, any viral myocarditis or any genetic cardiomyopathy or dilated cardiomyopathy, (3) the method of determining, ameliorating and treating any heart failure in a human patient comprising the steps of measuring the level of any cytokine, the level of endotoxin (LPS), TNFα and CD14 or any cytokine production in the blood of the patient, and if any such level is elevated, administering to the patient a therapeutically effective amount of any bile acid such as chenodeoxycholic acid, dehydrocholic acid and cholic acid, (4) the method mentioned above wherein the bile acid is able to inhibit any response by any cell to endotoxin (LSP), (the method mentioned above wherein the bile acid is able to decrease any cytokine production by any cell in response to endotoxin (lipopolysaccharide, LPS), (5) the said method wherein the bile acid such as ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid are able to reduce the permeability of the gut wall to bacteria and/or endotoxin (lipopolysaccharide, LPS), (6) the said method wherein the bile acid is administered orally, intravenously or rectally, (7) a method of reducing elevated levels of LPS in human blood of patients by administering any amount of bile acid selected from the group consisting of ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid, (8) the method of reducing elevated levels of LPS in human blood of patients by administering any amount of bile acid selected from the group consisting of ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid wherein the patients with cachexia due to liver cirrhosis, and (9) the method of reducing elevated levels of LPS in human blood of patients by administering any amount of bile acid selected from the group consisting of ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid wherein the bile acid is administered intravenously, rectally, or orally.

The specification discloses only a method of ameliorating or treating endotoxin-mediated immune activation in acute or chronic heart failure, the method comprising the steps of measuring the level of TNF-α, endotoxin, and soluble CD14 from blood sample taken from the patient, and

administering to the patient ursodeoxycholic acid or a combination of ursodeoxycholic acid and diuretics when the levels of TNF-α, endotoxin or soluble CD14 is elevated. The specification further discloses a method of reducing elevated levels of LPS induced TNF-α in human by administering ursodesoxycholic acid to the human patient with cachexia due to liver cirrhosis (page 45, Example 12).

With the exception of the specific method mentioned above, the specification as filed does not adequately describe the other elevated cytokines, inflammatory markers or production to be measured by the claimed method. Further, there is inadequate written description about the relationship between various cytokines, inflammatory markers and its production associated with any and all heart failure, any heart failure such as coronary artery disease, valvular disease, hypertrophic obstructive cardiomyopathy, viral myocarditis, genetic cardiomyopathy or dilated carciomyopathy. There is a lack of disclosure about administering any bile acid such as chenodeoxycholic acid, dehydrocholic acid and cholic acid to a human patient would ameliorate or treat any heart failure. There is a lack of disclosure of administering any ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid would reduce the elevated levels of lipolysaccharide (LPS) in human blood of any patient, any patient with cachexia due to liver cirrhosis.

The specification discloses administering only ursodesoxycholic acid as a method of reducing LPS-mediated increase in TNF production in patient with chronic heart failure with edema or with cardiac cachexia or cachexia due to liver cirrhosis, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of bile acids, cytokines, inflammatory markers to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 9/23/05 have been fully considered but are not found persuasive.

Applicants' position is that claim 1 has been amended to recite the specific bile acid and no longer reads on preventing heart failure comprising administering to the patient any or all

compound. There is adequate description in the specification for the three additionally claimed bile acids (compared to UDCA). It should be noted that one skilled in the art would recognize that each of the three additionally claimed bile acids (compared to UDCA) can be used in equal measure, due to their close structural and functional similarity.

In response, the specification discloses administering only ursodesoxycholic acid as a method of reducing LPS-mediated increase in TNF production in patient with chronic heart failure with edema or with cardiac cachexia or cachexia due to liver cirrhosis. With the exception of the specific method of ameliorating and treating endotoxin-mediated immune activation in acute and chronic heart failure with edema by measuring the elevated level of TNF-α from blood sample taken from the patient, and administering to the patient a therapeutically effective amount of ursodeoxycholic acid, the specification as filed does not adequately describe the other elevated cytokines, inflammatory markers or production to be measured by the claimed method. The relationship between various cytokines, inflammatory markers and its production associated with any and all heart failure, any heart failure such as coronary artery disease, valvular disease, hypertrophic obstructive cardiomyopathy, viral myocarditis, genetic cardiomyopathy or dilated cardiomyopathy is not adequately described. Further, there is a lack of disclosure about administering any bile acid such as chenodeoxycholic acid, dehydrocholic acid and cholic acid to a human patient would ameliorate or treat any heart failure. There is a lack of disclosure of administering any ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid and cholic acid would reduce the elevated levels of lipolysaccharide (LPS) in human blood of any patient, any patient with cachexia due to liver cirrhosis.

As explained above, despite of the closely related structures of the other three bile acid, Greve et al, PTO 1449, teach not all bile acids are capable of reducing LPS mediated TNF production. Greve et al teach DCA in the concentration used appeared to be a strong inhibitor of TNF release by human monocytes whereas CDCA is less effective and UDCA is not effective at any concentration (see page 456, col. 2, Results, Figure 1, page 456, Figure 2, in particular). Given the lack of any addition bile acid administered in the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of bile acid to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "inhibit the response by a cell to endotoxin" in claim 17 is ambiguous and indefinite because it is not clear which "response" by which "cell" to endotoxin is being inhibits by the bile acid in the claimed method. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "decrease the cytokine production by a cell in response to endotoxin" in claim 18 is ambiguous and indefinite because it is not clear which cytokine produced by which cell in response to endotoxin is being decrease by the bile acid in the claimed method. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 82-83 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,589,358 (Dec 31, 1996; PTO 892).

The '358 patent teaches a method of treating liver cirrhosis by administering to the human patients an effective amount of bile acid such as ursodesoxycholic acid (see col. 32, lines 36-53, in particular). The reference method of treating liver cirrhosis uses the same bile acid as claimed. Therefore, the reference method would inherently reduce the elevated levels of LPS in human blood. Thus, the reference teachings anticipate the claimed invention.

13. Claims 82-83 and 85 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,674,855 (Oct 7, 1997; PTO 892).

The '855 patent teaches a method of treating lipopolysaccharide (LPS) induced endotoxemia in humans by administering to the human subject an effective dose of bile acid such

as cholic acid (see col. 3, lines 55-57, col.10, lines 15-16, col. 9, lines 44, in particular). The reference cholic acid is administered intravenously or other forms of administration (see col. 10, line 37, col. 3, lines 48-50, in particular). Claim 83 is included in this rejection because LPS inherently caused cachexia. The reference method using the same bile acid inherently reduces the elevated levels of LPS in human blood since the reference method reduces the elevated level of inflammatory cytokine TNFα (see col. 5, line 42-52, Fig. 8 and 9, in particular). Thus, the reference teachings anticipate the claimed invention.

14. Claim 78 is rejected under 35 U.S.C. 102(b) as being anticipated by US 5,514,696 (May 7, 1996; PTO 892).

The '696 patent teaches a pharmaceutical composition comprising bile acid, diuretics and endothelin (see col. 6, line 3-15, lines 36-54, in particular). The term "comprising" is open-ended. It expands the claimed composition to include additional compound to read on the reference composition. Thus, the reference teachings anticipate the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 82 and 85-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,589,358 (Dec 31, 1996; PTO 892) in view of Gennaro et al (in Remington: The science and

practice of Pharmacy, pages 710-713, Mach publishing company, Eston, Pennsylvania 18042, 1995; PTO 892).

The teachings of the '358 patent have been discussed supra.

The invention in claim 85 differs from the teachings of the reference only in that the bile acid is administered intravenously.

The invention in claim 86 differs from the teachings of the reference only in that the bile acid is administered rectally.

The invention in claim 87 differs from the teachings of the reference only in that the bile acid is administered orally.

Gennaro et al teach oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) and rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics (see page 710, paragraph bridging col. 1 and 2, in particular). Gennaro et al teach intravenous route imposed no delay by absorption and the preferred route when an emergency calls for an immediate response (see page 711, col. 1, first full paragraph, in particular). The route of administration such as intravenously, rectally, or orally is within the purview of one of ordinary skill in the pharmaceutical art as taught by Gennaro et al.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer ursodesoxycholic acid to human for treating liver cirrhosis as taught by the '358 patent via intravenous route, oral route or rectal route as taught by Gennaro et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) while rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics (see page 710, paragraph bridging col. 1 and 2, in particular) and intravenous route imposed no delay by absorption and the preferred route when an emergency calls for an immediate response as taught by Gennaro et al (see page 711, col. 1, first full paragraph, in particular).

18. Claims 82 and 86-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,674,855 (Oct 7, 1997; PTO 892) in view of Gennaro et al (in Remington: The science and

practice of Pharmacy, pages 710-713, Mach publishing company, Eston, Pennsylvania 18042, 1995; PTO 892).

The teachings of the '855 patent have been discussed supra.

The invention in claim 86 differs from the teachings of the reference only in that the bile acid is administered rectally.

The invention in claim 87 differs from the teachings of the reference only in that the bile acid is administered orally.

Gennaro et al teach oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) and rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics (see page 710, paragraph bridging col. 1 and 2, in particular). The route of administration such as rectally, or orally is within the purview of one of ordinary skill in the pharmaceutical art as taught by Gennaro et al.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer cholic acid for treating lipopolysaccharide (LPS) induced endotoxemia in humans as taught by the '855 patent via oral route or rectal route as taught by Gennaro et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) while rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics (see page 710, paragraph bridging col. 1 and 2, in particular).

19. Claims 1-2, 6, 17-18, and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niebauer et al (Abstract from 71st scientific sessions of the American Heart Association, Dallas, Texas, USA November 8-11, 1998, page I27, PTO 1449) in view of US 5,674,855 (Oct 7, 1997; PTO 892) or Greve et al (Hepatology 10(4): 454-458, 1989; PTO 1449).

Niebauer et al teach a method of determining, ameliorating and treating chronic heart failure in human by measuring the level of cytokine such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα) or inflammatory marker such as endotoxin, soluble CD14, C-reactive protein

(CRP) and elevated level of the reference cytokine is successfully treated with diuretic (see abstract, in particular).

The claimed invention in claim 1 differs from the teachings of the reference only in that the method of treating heart failure by reducing the elevated level of inflammatory cytokine by administering bile acid wherein the bile acid is cholic acid or deoxycholic acid instead of diuretic.

The '855 patent teaches a method of treating lipopolysaccharide (LPS) induced endotoxemia in humans by administering to the human subject an effective dose of bile acid such as cholic acid (see col. 3, lines 55-57, col.10, lines 15-16, col. 9, lines 44, in particular). The reference cholic acid is administered intravenously or other forms of administration (see col. 10, line 37, col. 3, lines 48-50, in particular). Claims 25-27 are included in this rejection because the route of administration is within one of ordinary skill in the pharmaceutical art. The reference bile acid reduces the elevated level of inflammatory cytokine TNFα (see col. 5, line 42-52, Fig. 8 and 9, in particular).

Greve et al teach TNFα is an important mediator of endotoxin toxicity caused by LPS and bile acid such as deoxycholic acid is useful for inhibiting TNFα production and release by cells such as monocytes (see entire document, page 456, col. 2, Fig. 1, Discussion, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the diuretic in the method of treating chronic heart failure in human that have elevated level of TNFα as taught by Niebauer et al for the bile acid such as cholic acid that reduces TNFα as taught by the '855 patent or the bile acid such as deoxycholic acid that inhibits TNFα production and release by cell such as monocytes as taught by Greve et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Niebauer et al teach endotoxemia occurs in chronic heart failure in humans that resulted in elevated levels of cytokine such as TNFα and endotoxin can be normalized by diuretic treatment. The '855 patent teaches lipopolysaccharide (LPS) induced endotoxemia and cholic acid can reduce the elevated level of inflammatory cytokine such as TNFα (see col. 5, line 42-52, Fig. 8 and 9, in particular). Greve et al teach TNFα is an important mediator of endotoxin toxicity caused by LPS and bile acid such as deoxycholic acid is useful for inhibiting TNFα production and release (see entire document, page 456, col. 2, Fig. 1, Discussion, in particular).

20. Claims 21 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niebauer et al (Abstract from 71st scientific sessions of the American Heart Association, Dallas, Texas, USA November 8-11, 1998, page I27, PTO 1449) in view of US 5,674,855 (Oct 7, 1997; PTO 892) or Greve et al (Hepatology 10(4): 454-458, 1989; PTO 1449) as applied to claims 1-2, 6, 17-18, and 25-27 mentioned above and further in view of Schwarzenberg et al (Pediatr Res 35(2): 214-217, Feb 1994; PTO 892).

The combined teachings of Niebauer et al and the '855 patent or Greve et al have been discussed supra.

The claimed invention in claim 21 differs from the combined teachings of the references only in that the method of treating heart failure wherein the bile acid is able to reduce the permeability of the gut wall to bacteria and/or endotoxin (lipopolysaccharide, LPS).

The claimed invention in claim 53 differs from the combined teachings of the references only in that the method of treating heart failure wherein the bile acid is ursodeoxycholic acid (UDCA).

Schwarzenberg et al teach LPS can cross the intestinal barrier (gut wall) and administration of ursodeoxycholic acid (UDCA) can decrease the translocation of LPS and prevent the cytokine response as measured by TNF levels (see abstract, in particular). Schwarzenberg et al teach UDCA administered prophylactically might reduce the morbidity in clinical conditions leading to gut-derived endotoxemia (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the diuretic in the method of treating chronic heart failure in human that have elevated level of TNFα as taught by Niebauer et al for the bile acid such as ursodeoxycholic acid (UDCA) that reduce the permeability of gut wall to endotoxin (LPS) as taught by Schwarzenberg et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because ursodeoxycholic acid (UDCA) administered prophylactically might reduce the morbidity in clinical conditions leading to gut-derived endotoxemia as taught by Schwarzenberg et al. Niebauer et al teach chronic heart failure in human has elevated level of cytokine such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα) or inflammatory marker such as endotoxin.

21. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Niebauer et al (Abstract from 71st scientific sessions of the American Heart Association, Dallas, Texas, USA November 8-11, 1998, page I27, PTO 1449) in view of Bo et al (Biosci Biotechnol Biochem 59(4): 624-7, April 1995; PTO 892).

Niebauer et al teach a method of determining, ameliorating and treating chronic heart failure in human by measuring the level of cytokine such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα) or inflammatory marker such as endotoxin, soluble CD14, C-reactive protein (CRP) and elevated level of the reference cytokine is successfully treated with diuretic (see abstract, in particular).

The claimed invention in claim 1 differs from the teachings of the reference only in that the method of treating heart failure by reducing the elevated level of inflammatory cytokine by administering bile acid wherein the bile acid is chenodeoxycholic acid instead of diuretic.

Bo et al teach in the presence of LPS, administering physiological concentration of bile acid such as chenodeoxycholic acid inhibits the inflammatory cytokine production such as IgE by lymphocytes, suggesting that free bile acids can act as an anti-allergic agent (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the diuretic in the method of treating chronic heart failure in human that have elevated level of inflammatory cytoline as taught by Niebauer et al for the bile acid such as chenodeoxycholic acid that inhibit inflammatory cytokine production as taught by Bo et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because chenodeoxycholic acid can inhibit the production of inflammatory cytokine in the presence of LPS as taught by Bo et al (see abstract, in particular). Niebauer et al teach chronic heart failure in human has elevated level of inflammatory cytokine and endotoxin such as LPS (see abstract, in particular).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The

examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

24. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
November 10, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600